38. (New) A stable pharmaceutical unit dosage form which comprises an optically pure enantiomer of fluoxetine, or a pharmaceutically acceptable salt thereof, and one of more pharmaceutically acceptable excipients wherein said dosage form is not a capsule or gel cap.

## REMARKS

Claims 1-35, as amended, and new claims 36-38 are pending in this application for the Examiner's review and consideration. The specification and claim 7 have been amended to correct several typographical errors. Claim 16 has been amended to clarify that the tablet dissolves *and disperses uniformly* in *more than five minutes* when subjected to the DISSOLUTION TEST. *See, e.g.*, Specification at page 18, lines 18-25. Claim 21 has been amended to clarify that the *stable,* solid compressed tablet consists essentially of racemic fluoxetine, an optically pure enantiomer, or a pharmaceutically acceptable salt thereof, and microcrystalline cellulose and pre-gelatinized starch is stable. *See, e.g.*, Specification at page 5, lines 13-15. Claim 30 has been amended to recite a stable pharmaceutical unit dosage form that does not dissolve and disperse uniformly in less than three minutes when subjected to the DISSOLUTION TEST.

New claim 36 recites one embodiment that includes an anhydrous or non-hygroscopic pharmaceutical composition consisting essentially of an optically pure enantiomer of fluoxetine, or a pharmaceutically acceptable salt thereof; and at least one pharmaceutically acceptable excipient, wherein the composition is substantially free of unbound water. *See, e.g.*, Specification at page 11, lines 26-32. New claim 37 recites another embodiment that includes a stable solid compressed tablet that dissolves and disperses uniformly in more than five minutes when subjected to the DISSOLUTION TEST. *See, e.g.*, Specification at page 18, lines 18-25. New claim 38 recites a stable pharmaceutical unit dosage form which comprises an optically pure enantiomer of fluoxetine, or a pharmaceutically acceptable salt thereof, and one of more pharmaceutically acceptable excipients wherein said dosage form is not a capsule or gel cap. These amendments are supported by the specification and claims as originally filed such that no new matter has been added.

The abstract was objected to because it was not commensurate in scope with the specification. A substitute abstract sheet is attached hereto. Thus, the objection has been overcome and should be withdrawn.

**The Invention**

Applicants have discovered, and are claiming, novel solid pharmaceutical compositions of racemic or optically pure fluoxetine. Certain of the solid compositions claimed have improved chemical stability over compositions disclosed in the art cited by the Examiner, particularly over the lactose-containing compositions known in the art. These novel, stable compositions may be in tablet form and are lactose-free, anhydrous, non-hygroscopic, or a combination thereof.

It is helpful to discuss what is specifically recited in claims 1-38. Claims 1-12 are directed to *lactose-free* pharmaceutical compositions containing *an optically pure enantiomer* of fluoxetine, or a pharmaceutically acceptable salt thereof; and at least one non-lactose pharmaceutically acceptable excipient. Claims 13-20, 22 and 37 are directed to *chemically stable compressed tablets* free of lactose that contain *racemic* fluoxetine or an *optically pure enantiomer* of fluoxetine; and at least one pharmaceutically acceptable excipient. Claim 21 is directed to a *stable,* solid compressed tablet consisting essentially of *racemic* fluoxetine or an *optically pure enantiomer* of fluoxetine, and microcrystalline cellulose and pre-gelatinized starch. Claims 23-29 are directed to *anhydrous* solid pharmaceutical compositions containing *racemic* or an *optically pure enantiomer* of fluoxetine; and one or more pharmaceutically acceptable excipients. Claims 30-32 and new claim 38 are directed to *stable* solid pharmaceutical unit dosage forms containing *racemic* fluoxetine or an *optically pure enantiomer* of fluoxetine; and one or more pharmaceutically acceptable excipients wherein the dosage form is not a capsule or a gel cap. Claim 33 and 34 are directed respectively to solid compressed *tablets* and disintegrating *tablets*, each of which are *substantially free of lactose* and contain an *optically pure enantiomer* of fluoxetine, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient which is not lactose. Claim 35 is directed to a method of treating depression in a mammal by administration of one of the novel compositions claimed above. New claim 36 is directed to an *anhydrous or non-hygroscopic* pharmaceutical composition consisting essentially of an *optically pure enantiomer* of fluoxetine; and at least one pharmaceutically

acceptable excipient, wherein the composition is *substantially free of unbound water*. New claim 37 is directed to a *stable solid compressed tablet* that dissolves and disperses uniformly in more than five minutes when subjected to the DISSOLUTION TEST.

The Examiner has not cited a reference that discloses a pharmaceutically useful composition or dosage form that is in tablet form, lactose-free, anhydrous, or non-hygroscopic, as claimed herein, nor has the Examiner cited any art that suggests the chemical stability of the claimed compositions compared to those in the cited art.

Applicants' claimed invention must be considered in light of the incompatibility of the most common pharmaceutical excipient–lactose–with amine containing compounds, such as fluoxetine and the optically pure enantiomers thereof. Further, the claimed invention must be considered in view of the fact that the most common or conventional dosage form for oral delivery is a tablet. Conventional tablet formulations are *not* anhydrous or non-hygroscopic, even if manufactured in "moisture-proof packaging," as a result of the difficulties associated with the manufacture, storage, or handling of such compositions. Thus, the art, including the cited art, teaches the use of lactose and does not disclose or suggest the use of lactose-free, anhydrous, or non-hygroscopic formulations, nor does the cited art disclose or suggest such compositions in tablet form. Clearly, when considered as a whole, the art *teaches away* from that which Applicants claim.

**The Rejections Under 35 U.S.C. § 112 Should be Withdrawn**

Claims 12, 33, and 34 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite for the reasons set forth on page 3 of the Office Action. In particular, the Examiner contends that the phrase "substantially free of mono or di-saccharides/lactose" is relative and renders the claim indefinite. Further, the Examiner contends that the term "substantially free" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

On the contrary, Applicants submit that the term "substantially free" is distinctly and concisely defined in the Specification at page 16, lines 16-19, which states:

> The term "substantially free" means less than 5 weight percent, preferably less than about 2 weight percent, and more preferably less than about 1 weight percent.

Thus, it is clear to one of ordinary skill in the art that "substantially free" of mono or di-saccharides/lactose refers to compositions having such parameters.

Further, the Examiner contends that the claims are even more indefinite by the limitation on lines 4-5 of claims 33 and 34, where it is claimed that the pharmaceutically acceptable excipient cannot be lactose. Applicants respectfully traverse. A composition can be "substantially free" of lactose and contain "at least one excipient that is not lactose," *e.g.*, if lactose is present as an impurity when the composition is prepared. Applicants do not believe this language is confusing, particularly to one of ordinary skill in the art, and respectfully request that the Examiner withdraw the rejection.

Claims 1, 13-20, and 35 were also rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the reasons set forth on page 3 of the Office Action. In particular, the Examiner contends that the phrases "free of lactose" and "lactose-free" are unclear and contradict the language of the specification. The Examiner states:

> On its face, the phrases "lactose free" or "free of lactose" mean there is no lactose present in the the claimed pharmaceutical compositions. Yet, in the specification, at page 15, Applicant states that lactose may be present in the claimed compositions but in amounts that won't detrimentally affect the claimed composition.

Applicants respectfully traverse. There is no confusion as to the use of these terms in the specification or claims. Applicants refer the Examiner to the discussion of the claims above, which clarifies that different embodiments are claimed where lactose is included or excluded as a potential ingredient. Further, Applicants have defined "lactose-free" in the Specification at page 15, lines 16-23. The term "free of lactose," as used in the application, includes compositions without lactose, as well as those "*substantially free* of lactose," in which "substantially free" has been discussed above.[1] Moreover, Applicants have clearly defined the amount of lactose that is acceptable using a functional standard for ascertaining the requisite amount of lactose:

> The term "lactose-free" as used herein is intended to mean that the amount of lactose present, if any, in the dosage form of fluoxetine or its enantiomers is insufficient to cause the incompatibility between fluoxetine or salts or enantiomers thereof and lactose discovered by the inventors detrimentally

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[1] Applicants note that claims 23, 25, 26, 27, and 28 recite formulations that may include lactose, as these claims are directed to stable anhydrous and non-hygroscopic formulations.

affect the potency of the fluoxetine below about 90% of initial potency over the shelf life of the dosage form.

Thus, Applicants respectfully submit that those of ordinary skill in the art can readily determine the maximum acceptable amount of lactose, particularly in view of the guidance provided by the specification.

Moreover, claim 34 was objected to under 37 C.F.R. § 1.75 as being a substantial duplicate of claim 33. However, claims 33 and 34 recite different preambles, each of which is distinct and understood as such by one of ordinary skill in the art. The preamble reciting "[a] solid compressed tablet substantially free of lactose" in claim 33 is understood by one of ordinary skill in the art to mean solid tablets substantially free of lactose that are made by *pressing* the ingredients to form the tablets with the use of compression equipment. *See, e.g.*, Specification at page 31, line 31 to page 32, line 12. However, the preamble reciting "[a] disintegrating tablet substantially free of lactose" in claim 34 will be understood by one of ordinary skill in the art to mean tablets that disintegrate, or be reduced to particles, when exposed to an aqueous environment whether *in vitro* or *in vivo* and require *more* than three minutes to dissolve and disperse uniformly. *See, e.g.*, Specification at page 18, lines 18-25 and at page 22, lines 4-6. Further, it is stated in the Specification at page 22, line 33 to page 23, line 2 that disintegrants are specifically *excluded* from the composition, or are present in amounts sufficient to prevent rapid dissolving of water; for example, *compressed* tablets that are free of lactose are preferably non-dispersible tablets," clearly distinguishing compressed tablets from disintegrating tablets. Although a tablet may be disintegrating or compressed, it is clear that the claim terms are not identical and therefore not duplicative. Thus, Applicants respectfully request that the objection under 37 C.F.R. § 1.75 should be reconsidered and withdrawn.

**The Rejection Under 35 U.S.C. §102(b) Should Be Withdrawn**

Claims 13-14, 16-18, 21-25, 28-30, and 35 were rejected under 35 U.S.C. § 102(b) as being anticipated by European Patent Application EP 0 693 281 A2 to Mendizabal ("Mendizabal") for the reasons set forth on page 4 of the Office Action. Applicants respectfully traverse the rejection for the reasons set forth below.

Mendizabal discloses pharmaceutical compositions that contain racemic fluoxetine, or an acid addition salt thereof, suitable for manufacturing dispersible tablets by

direct compression and further including excipients and coadjuvants. These tablets, which require a disintegrant, are characterized by their speed of disintegration in water, *i.e.*, within three minutes in water at 19°C - 21°C. *See, e.g.*, Mendizabal at page 5, lines 40-41. On the contrary, the compositions of the claimed invention require more than three minutes to dissolve and disperse uniformly in the DISSOLUTION TEST as expressly discussed in the Specification at page 18, lines 18-25. In particular, the language "a chemically stable compressed tablet" as used in claims 13-14, 16-18, and 21-22 when read in light of the specification, refers to formulations that do not dissolve and disperse uniformly in less than three minutes. *Id.* Further, claim 30 specifically recites formulations that do not dissolve and disperse uniformly in less than three minutes and claims 16 and 37 specifically recite formulations that dissolve and disperse uniformly in more than five minutes. For this reason alone, Mendizabal fails to disclose each and every element of the claims 13-14, 16-18, 21-22, and 30. Thus, claims 13-14, 16-18, 21-22, and 30 are not anticipated by Mendizabal.

Further, although Mendizabal discloses racemic fluoxetine formulations both with and without lactose, as a whole Mendizabal is silent as to any benefit to using lactose-free formulations; while Applicants have found that lactose-free formulations are unexpectedly stable chemically. Indeed, Mendizabal fails to recognize the instability of fluoxetine and lactose, particularly in the presence of water. Contrary to Mendizabal, the present invention claims *stable* lactose-free compositions and dosage forms containing fluoxetine or an optically pure enantiomer thereof (*See, e.g.*, claims 13-14, 16-18, 21-22, and 37-38). In addition, claim 21 recites the language *consisting essentially of*, which excludes all ingredients that materially affect the basic and novel characteristics of the invention, *i.e.*, a stable formulation. Thus, claim 21 excludes amounts of lactose or water from the composition of the tablet that would render it unstable. New claim 36 contains similar recitations. Thus, for these additional reasons, claims 13-14, 16-18, 21-22, and 37-38 are not anticipated by Mendizabal.

Furthermore, claims 22-25, 28-29, and 36 recite *anhydrous* or *non-hygroscopic formulations*, *e.g.*, formulations that are substantially free of unbound water (*See, e.g.*, Specification at page 10, lines 16-25 and page 11, lines 6-25). Mendizabal, however, is silent–at best–as to the use of anhydrous or non-hygroscopic formulations of fluoxetine. Indeed, the incompatibility of fluoxetine, lactose, and moisture is not disclosed by Mendizabal. Furthermore, Mendizabal discloses formulations, and uses conventional

methods of preparing such formulations, that fail to take precautions against the presence of water. Indeed, Mendizabal uses conventional direct compression to avoid *additional* external water from the atmosphere, thus admitting use of water. *See, e.g.*, Mendizabal at page 5, lines 26-31. Moreover, Mendizabal does *not* disclose a drying process, which would ensure that each component is itself substantially free of unbound water (*See, e.g.*, Mendizabal at page 5, lines 26-31). Thus, claims 22-25, 28-29, and 36 are not anticipated by Mendizabal.

Furthermore, Mendizabal does not disclose chemically stable, anhydrous, or non-hygroscopic fluoxetine formulations that dissolve and disperse in *greater* than three minutes in the DISSOLUTION TEST. This is precisely what is covered by claims 13-14, 16-18, 22-25, 28-30, and 35. Thus, these claims cannot be anticipated by Mendizabal.[2]

For all the above reasons, Applicants respectfully submit that the claims are not anticipated by Mendizabal and request that the rejection under 35 U.S.C. § 102(b) be reconsidered and withdrawn as to all claims.

**The Rejection Under 35 U.S.C. §103(a) Should Be Withdrawn**

Claims 1-35 were rejected under 35 U.S.C. § 103(a) as being obvious over Mendizabal in view of the Physicians Desk Reference ("the PDR"), 50th ed. (1996) for reasons set forth on page 5 of the Office Action. Applicants respectfully traverse the rejection for the reasons set forth below.

Mendizabal does not disclose, much less suggest, chemically stable, anhydrous, or non-hygroscopic formulations containing racemic fluoxetine, and an optically pure enantiomer of fluoxetine, or a pharmaceutically acceptable salt thereof. In addition, Mendizabal does not disclose or suggest the unexpected benefits of lactose-free formulations or formulations that disintegrate in greater than three minutes. On the contrary, the claimed invention recites lactose-free formulations (*See, e.g.*, claims 1-22, 24, 33-34, and 36-37), anhydrous or non-hygroscopic formulations (*See, e.g.*, claims 22-29 and 36), formulations that dissolve and disperse in greater than three minutes (*See, e.g.*, claims 13-22, 30-32, and

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[2] Claim 29 is dependent on claims 1, 13, 14, 21, 23, and 24, each of which are not anticipated by Mendizabal for the reasons above. In addition, claim 35 is dependent on claims 13-14, 21, 23-24, and 30, each of which are not anticipated by Mendizabal for the reasons above. Thus, claims 29 and 35 cannot be anticipated by Mendizabal.

33-34), and methods using such formulations for the treatment of depression (*See, e.g.*, claim 35).

The PDR fails to remedy the deficiencies of Mendizabal. The PDR only discloses Pulvule® capsules that contain racemic fluoxetine hydrochloride, FD&C Blue No. 1, gelatin, iron oxide, silicone, starch, titanium dioxide, and other ingredients, as solid oral formulations. The claims 13-22, 25, 33-34, and 37 are not directed to *capsules* but to solid *tablet* formulations. Thus, the PDR fails to teach or suggest lactose-free tablets. Claims 13-22, 25, 33-34, and 37, for example, recite tablet formulations that are substantially free of lactose.

In addition, the PDR is silent as to the benefits of lactose-free tablet formulations. This is not surprising because the PDR refers only to solid capsule formulations. Indeed, there is no mention in the PDR of tablet formulations or instability problems associated with lactose and fluoxetine in tablets. On the contrary, the claimed invention claims compressed tablets, as opposed to capsules that readily use and/or require the use of lactose which is well known, inexpensive, highly pure, and have excellent compression characteristics.

Moreover, the PDR does not disclose or suggest anhydrous or non-hygroscopic formulations containing racemic fluoxetine, an optically pure enantiomer of fluoxetine, or a pharmaceutically acceptable salt thereof. On the contrary, claims 22-28 and 36 recite such anhydrous formulations and/or non-hygroscopic formulations. Indeed, Mendizabal and the PDR both fail to disclose or suggest such anhydrous or non-hygroscopic formulations, as presently recited in claims 22-28 and 36.

Further, the PDR, as well as Mendizabal, fail to disclose or suggest formulations containing an optically pure enantiomer of fluoxetine, as presently recited in claims 1-12, 19-20, 26-27, 31-34, and 36. Although the PDR discloses that both fluoxetine enantiomers have essentially equivalent pharmacologic activity, it does not disclose formulations prepared with either enantiomer. Thus, even if the presently recited lactose-free formulations of racemic fluoxetine were known, *arguendo*, one of ordinary skill in the art in view of the PDR would not have been motivated at the time of this invention to prepare pharmaceutical formulations that contained only an optically pure enantiomer of fluoxetine. Thus, at best, the cited references may render the optically pure enantiomer "obvious to try." This is not, however, the proper test for obviousness. *See, e.g., Hybritech, Inc. v. Monoclonal*

*Antibodies, Inc.*, 802 F.2d 1367, 1380 (Fed. Cir. 1986). For these reasons, claims 1-12, 19-20, 26-27, 31-34, and 36 are not disclosed or suggested by the cited references.

The Examiner also alleges that it would be obvious and well within the capability of the skilled artisan not to use a disintegrant in the claimed composition. However, Mendizabal discloses dispersible tablets that completely disintegrate within three minutes in water at 19°C-21°C and the disintegration rate is *dependent* on the use of disintegrants, as discussed above. *See, e.g.*, Mendizabal at page 5, lines 40-41. Indeed, Mendizabal is directed to dispersible tablets that have *rapid disintegration* in water. *See, e.g.*, Mendizabal at page 2, line 12-16. Indeed, the presently recited pharmaceutical compositions should be understood to disintegrate and disperse the active ingredient in greater than three minutes, as discussed above. *See, e.g.*, Specification at page 18, lines 18-25. Thus, Mendizabal clearly *teaches away* from the present invention. Moreover, claim 15 recites a formulation that excludes disintegrants from the composition to *prevent* rapid dissolution in water, claim 30 recites compressed tablets that do not dissolve and disperse uniformly in less than three minutes, and claims 16 and 37 recite compressed tablets that dissolve and disperse uniformly in more than five minutes, when subjected to the DISSOLUTION TEST. Additionally, claim 21 recites the language "consisting essentially of," which excludes the rapid disintegrants of Mendizabal, particularly in view of the specification.

Furthermore, Mendizabal and the PDR relate to distinct formulations made for different purposes. In particular, Mendizabal is directed to rapidly disintegrating compressed *tablets*, while the PDR is directed to Pulvule® *capsule* formulations. In other words, one of ordinary skill in the art aware of these two cited references at the time of the invention would not have been motivated to combine the rapidly dispersing formulations of Mendizabal with the capsule formulation in the PDR. Even when combined, the references do *not* disclose or suggest the improved stability of the claimed compositions, much less even recognize the problem with lactose-containing tablets. Thus, there would be no motivation to prepare a lactose-free compressed tablet when capsule technology is combined with disintegrating tablet technology.

In addition, the combination of these references would lead one of ordinary skill in the art to formulations that disintegrate in less than three minutes. The present invention, however, recites tablets and compositions that are understood to not rapidly disintegrate in less than three minutes. For the foregoing reasons, Mendizabal and the PDR,

whether taken alone or in combination, do not disclose or suggest the claimed invention. Thus, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn as to all claims.

Claims 1-35 were rejected under 35 U.S.C. § 103(a) as being obvious over Mendizabal in view of the PDR, and further in view of Wirth *et al.*, *J. Pharm. Sci.*, **87(1)**:31-39, 1998 ("Wirth"). Applicants respectfully traverse the rejection for the reasons set forth below.

Although Wirth discloses that tablets containing fluoxetine are unstable since fluoxetine undergoes the Maillard reaction with lactose, Wirth does not remedy the deficiencies of Mendizabal or the PDR. Wirth confirms what Applicants stated above–racemic fluoxetine is generically formulated with lactose throughout much of the world (Wirth at page 31, col. 2, lines 16-19 and Abstract). Moreover, Wirth does not disclose, much less suggest, pharmaceutical compositions that a) are anhydrous or non-hygroscopic or b) contain an optically pure enantiomer of fluoxetine. On the contrary, Applicants recite stable pharmaceutical compositions that are anhydrous or non-hygroscopic, contain an optically pure enantiomer of fluoxetine, and are in tablet form, such as recited in claims 1-29, 31-34, and 36-37.

Furthermore, Mendizabal and Wirth relate to formulations made for different purposes. Mendizabal is only concerned with tablet formulations that *rapidly* disperse, whereas Wirth is directed to *conventional* lactose-containing tablets as compared to the specific Pulvule® capsule formulation. In other words, one of ordinary skill in the art aware of these two cited references at the time of the invention would *not* have been motivated to combine the rapidly dispersing formulations of Mendizabal with the formulations tested in Wirth. Even when combined, the references do not suggest lactose-free tablets that disintegrate in greater than three minutes. The present invention, however, recites compositions that are understood to not rapidly disintegrate in less than three minutes.

Wirth also fails to remedy the deficiencies of Mendizabal and the PDR, since the cited references fail to disclose or suggest the recited formulations of an optically pure isomer of fluoxetine, as well as failing to disclose or suggest anhydrous or non-hygroscopic formulations.

In sum, Mendizabal, the PDR, and Wirth, whether taken individually or in any combination, do not disclose or suggest chemically stable, lactose-free, anhydrous, or non-

hygroscopic formulations containing racemic fluoxetine, an optically pure enantiomer of fluoxetine, or a pharmaceutically acceptable salt thereof which further dissolve or disperse uniformly in greater than three minutes as presently claimed. Further, since there is no motivation to combine Mendizabal and the PDR or Mendizabal and Wirth, as discussed above, there is no motivation to combine Mendizabal with the PDR and with Wirth. For all the reasons discussed herein, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) as to all claims.

## CONCLUSION

Applicants respectfully request the entry of the foregoing amendments and remarks into the file of the above-captioned application. Applicants believe that all pending claims are now in condition for allowance, early notice of which would be appreciated. Should the Examiner deem it helpful, a personal or telephone interview is respectfully requested to discuss any remaining issues in an effort to expeditiously advance the application to allowance.

Respectfully submitted,

Date: June 22, 1999

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Enclosures

## ABSTRACT

The present invention encompasses stable solid pharmaceutical dosage forms of fluoxetine, or its enantiomers or salts that are chemically and physically stable, high performance compositions which avoid any incompatibility between the active secondary amine containing compounds, and certain excipients including, but not limited to, lactose.